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Criofolinine and Vernavosine, New Pentacyclic Indole Alkaloids Incorporating Pyrroloazepine and Pyridopyrimidine Moieties Derived from a Common Yohimbine Precursor

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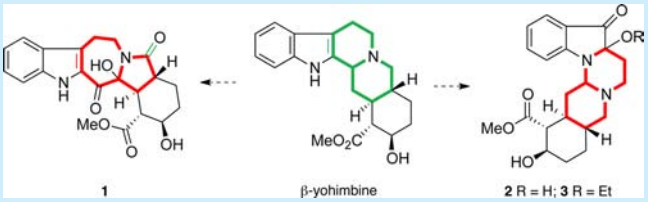
Supporting Information

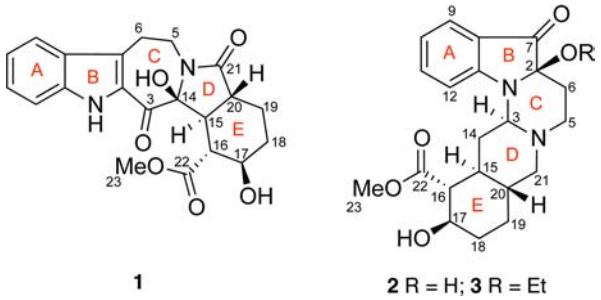
ABSTRACT: Two new indole alkaloids characterized by previously unencountered natural product skeletons, viz., criofolinine (**1**), incorporating a pyrroloazepine motif within a pentacyclic ring system, and vernavosine (**2**, isolated as its ethyl ether derivative **3**, which on hydrolysis regenerated the putative precursor alkaloid **2**), incorporating a pyridopyrimidine moiety embedded within a pentacyclic carbon framework, were isolated from a Malayan *Tabernaemontana* species. The structures and absolute configuration of these alkaloids were determined on the basis of NMR and MS analysis and confirmed by X-ray diffraction analysis.



Plants belonging to the genus *Tabernaemontana* have a pantropical distribution,[1] are rich in alkaloids,[2] and continue to provide alkaloids with diverse structures and a wide range of biological activities.[2−9] We previously reported the isolation and structure determination of two monoterpenoid indole alkaloids, voatinggine and tabertinggine, characterized by previously unknown natural product carbon skeletons derived from a common cleavamine-type precursor, from a Malayan *Tabernaemontana*.[9] We now report the isolation and structure determination of two additional minor alkaloids, representing first members of new structural groups of the monoterpenoid indoles, from the same plant (*T. corymbosa* Roxb. ex Wall).

Criofolinine (**1**) was initially obtained as a light yellowish oil and subsequently crystallized from absolute ethanol as colorless block crystals, mp >190 °C dec, with $[\alpha]^{25}_{D}$ +87 ($CHCl_3$, *c* 0.3). The IR spectrum showed bands due to NH/OH (3393 cm^{-1}) and various carbonyl (1699, 1648 cm^{-1}) functions, while the UV spectrum showed characteristic 2-acylindole absorption maxima at 205, 238, and 316 nm (log ε 4.67, 4.35, and 4.41 respectively).[10] The ESIMS showed an $[M + H]^+$ peak at *m*/*z* 399, and HRESIMS measurements ($[M + H]^+$ 399.1550) established the molecular formula as $C_{21}H_{22}N_2O_6$.[11]

The ^{1}H NMR data (Table 1) showed the presence of four aromatic resonances (δ 7.17−7.61), an indolic NH (δ 8.94), and a methoxy corresponding to a methyl ester group (δ 3.88). The ^{13}C NMR data (Table 2) showed a total of 21 carbon resonances, comprising one methyl, four methylene, eight methine, and eight quaternary carbon atoms. The resonance at



δ 191.8 was due to a conjugated ketone carbonyl and can be readily assigned to C-3, as it is part of the acyl indole moiety. Two other carbonyl resonances were observed at δ 173.5 and 174.2, which were assigned to ester and lactam carbonyl functionalities, respectively. Assignment of the former resonance to the ester carbonyl was facilitated by the observed three-bond correlation from the ester methyl to the carbonyl resonance at δ 173.5 in the HMBC spectrum. The carbon resonances of the indole unit can be readily assigned based on analogy with other 2-acylindole alkaloids[10a,12] and these assignments were readily corroborated by NOE and 2D NMR data. A downfield resonance at δ 92.2 was characteristic of a quaternary carbon linked to a nitrogen and an oxygen atom,[13] while another resonance at δ 73.3 was due to an oxymethine.

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Table 1. ^{1}H NMR Spectroscopic Data (δ) for 1−3 (600 MHz, $CDCl_3$)

H	1	2	3
3		4.22 dd (11, 3)	4.55 dd (12, 3)
5α	4.31 ddd (14, 4, 2)	2.46 ddd (12, 7, 4)	2.48 ddd (12, 5, 3)
5β	3.23 ddd (14, 12, 2)	3.32 ddd (12, 9, 6)	3.42 td (12, 3)
6α	3.42 ddd (18, 12, 4)	1.79 ddd (14, 9, 7)	1.70 ddd (14, 12, 5)
6β	3.11 dt (18, 2)	2.14 ddd (14, 6, 4)	2.06 dt (14, 3)
9	7.61 dd (8, 1)	7.61 dd (8, 1)	7.59 dd (7, 1)
10	7.17 ddd (8, 6, 2)	6.82 ddd (8, 7, 1)	6.81 t (7)
11	7.40 m	7.50 ddd (8, 7, 1)	7.51 ddd (8, 7, 1)
12	7.41 m	6.74 d (8)	6.86 d (8)
14α		1.70 dt (12, 3)	1.41 dt (12, 3)
14β		2.01 dt (12, 11)	2.26 q (12)
15	2.01 t (12)	1.54 m	1.53 m
16	2.68 dd (12, 10)	2.22 t (11)	2.22 t (11)
17	3.76 td (10, 3)	3.85 td (11, 4)	3.87 td (11, 4)
18β	1.45 tdd (13, 10, 3)	1.42 tdd (13, 11, 4)	1.45 tdd (13, 11, 4)
18α	2.14 dq (13, 3)	2.10 dq (13, 4)	2.12 dq (13, 4)
19α	1.30 tdd (13, 12, 3)	1.09 qd (13, 4)	1.05 qd (13, 4)
19β	2.20 dq (13, 3)	1.67 dq (13, 4)	1.62 dq (13, 4)
20	2.52 td (12, 3)	1.51 m	1.53 m
21α		2.40 dd (13, 11)	2.61 dd (14, 11)
21β		2.96 dd (13, 3)	2.92 dd (14, 3)
23	3.88 s	3.73 s	3.73 s
24			3.28 q (7)
24′			3.32 q (7)
25			1.19 t (7)
*N*H	8.94 br s		

Table 2. ^{13}C NMR Spectroscopic Data (δ) for 1−3

C	1[a]	2[a]	3[b]	C	1[a]	2[a]	3[b]
2	128.5	85.7	89.3	15	50.2	41.9	43.0
3	191.8	71.7	69.4	16	50.8	57.0	57.5
5	38.9	43.6	41.3	17	73.3	71.9	71.6
6	27.1	31.3	31.5	18	34.3	34.0	34.1
7	126.2	199.9	200.4	19	22.4	27.5	27.6
8	127.4	118.1	119.1	20	42.3	35.1	32.9
9	121.5	125.8	125.3	21	174.2	59.4	59.3
10	121.1	119.1	119.1	22	173.5	174.7	174.7
11	127.8	138.2	138.3	23	52.2	51.9	51.7
12	112.3	109.3	109.8	24			59.3
13	137.7	157.8	159.1	25			14.7
14	92.2	32.9	29.2				

[a]$CDCl_3$, 150 MHz. [b]$CDCl_3$, 100 MHz.

The COSY spectrum (Figure 1) showed two partial structures, an NCH_2CH_2 and a CH−CH−CH−CH−CH_2−CH_2 fragment, corresponding to a cyclohexane moiety. The assignment of the NCH_2CH_2 fragment to C-5−C-6 was supported by the three-bond correlations from H-6 to C-2, C-8, and from H-5 to C-7, in the HMBC spectrum (Figure 1). The lactam carbonyl was deduced to be linked to N-4, from the observed H-5 to C-21 three-bond correlation. The same applies to the oxygen- and nitrogen-linked C-14 from the observed H-5 to C-14 correlation. The correlation from H-15 to the ketone carbonyl C-3, and from H-16 to C-14, indicated that the carbinol amine C-14 was linked to C-3.

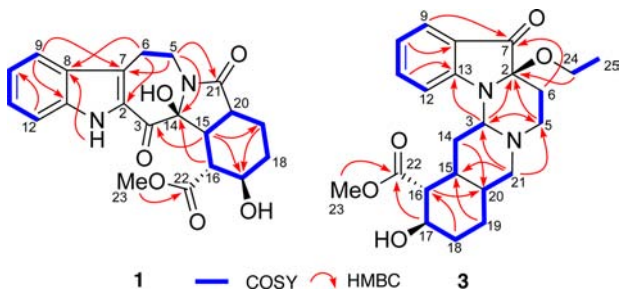

Figure 1. COSY and selected HMBCs of 1 and 3.

Consideration of the ^{1}H and ^{13}C chemical shifts allow the cyclohexane fragment to be rewritten as an CH(C═O)−CH−CH(CO_2Me)−CH(OH)−CH_2−CH_2− corresponding to C-20−C-15−C-16−C-17−C-18−C-19. This six-membered ring E must therefore be linked to the lactam C-21 via C-20 and to the carbinol amine C-14 via C-15, which completes assembly of the 6/5/7/5/6 pentacyclic ring system of criofolinine (1).

The relative configurations at the various stereogenic centers were established from the NOE data and the observed vicinal coupling constants. The D/E ring junction stereochemistry was deduced to be *trans* from the observed J_{15-20} value of 12 Hz (H-15 and H-20 *trans*-diaxial). The reciprocal NOEs observed for H-16/H-18, H-16/H-20, H-18/H-20, and for H-15/H-17, H-15/H-19, H-17/H-19, indicated that these hydrogens are axially oriented, which were consistent with a chair conformation adopted by the E-ring with the OH and CO_2Me substituents equatorially oriented (Figure 2). This was also in agreement with the observed J_{15-16} and J_{16-17} values of 12 and 10 Hz, respectively. The configuration at the carbinol amine C-14 could not be assigned with certainty based on the spectroscopic data alone but was nonetheless eventually established from X-ray analysis of 1, which also provided confirmation of the structure (Figure 2, relative configuration) of this novel alkaloid deduced from the spectroscopic data.[14]

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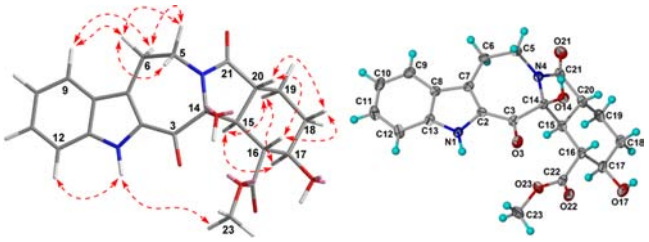


Figure 2. Selected NOEs and X-ray crystal structure of **1**.

Criofolinine (**1**) represents a new monoterpenoid indole alkaloid skeleton, incorporating a pyrroloazepine motif within a pentacyclic ring system.

Vernavosine (**2**) was isolated as its ethyl ether derivative (**3**), which was obtained as a yellow-green fluorescent oil, with $[\alpha]^{25}_{D}$ −49 ($CHCl_3$, *c* 0.31). The UV spectrum showed absorption maxima at 233, 257, and 396 nm, somewhat reminiscent of alkaloids possessing pseudoindoxyl chromophores,[10b,15] while the IR spectrum showed bands due to OH (3416 cm^{-1}) and various carbonyl (1712 cm^{-1}) functions. The ESIMS showed a $[M + H]^+$ peak at *m*/*z* 415, and HRESIMS measurements ($[M + H]^+$ 415.2233) established the molecular formula as $C_{23}H_{30}N_2O_5$.[16]

The ^{1}H NMR spectrum of **3** (Table 1) showed the presence of four aromatic resonances associated with the indole moiety (δ 6.81−7.59), a methine linked to two nitrogen atoms (δ 4.55), an oxymethine (δ 3.87), a methyl singlet (δ 3.73) due to methyl ester group (δ_C 51.7, 174.7), and an ethoxy side chain (δ_H 1.19, δ_C 14.7; δ_H 3.28, 3.32; δ_C 59.3). The notable absence of the characteristic indolic NH signal indicated substitution at the indolic nitrogen (N-1). The ^{13}C NMR data (Table 2) showed a total of 23 carbon resonances, comprising two methyl, seven methylene, nine methine, and five quaternary carbon atoms. Two carbonyl resonances were observed at δ 200.4 and 174.7, the former was due to a conjugated ketone, while the latter was assigned to the ester carbonyl. The ketone carbonyl was deduced to be at C-7 from the three-bond correlation from H-9 in the HMBC spectrum. In addition, an oxymethine resonance was seen at δ 71.6, while the resonance at δ 89.3 was due to a quaternary carbon linked to a nitrogen, and an oxygen atom.[13] This carbon corresponded to C-2 to which the ethoxy substituent is linked from the observed three-bond correlation from the ethoxy methylene hydrogens (H-24) to this carbon in the HMBC spectrum. The resonance at δ 69.4, which was associated with the ^{1}H resonance at δ 4.55, provided additional support for the presence of an aminal carbon.

The COSY spectrum showed in addition to the aromatic and ethoxy moieties, two other partial structures, NCH_2CH_2 and $NCHCH_2CHCHCHCH_2CH_2CHCH_2$ (Figure 1). The former two-carbon fragment corresponded to C-5−C-6 from the three-bond correlation from H-5 to C-2 observed in the HMBC spectrum (Figure 1). The nine-carbon fragment corresponded to C-3−C-14−C-15−C-16−C-17−C-18−C-19−C-20−C-21. The aminal carbon, C-3 (δ_H 4.55; δ_C 69.4) was linked to both N-1 and N-4, while the assignments of the methyl ester-substituted C-16 and hydroxy-substituted C-17, were consistent with the corresponding carbon resonances observed at δ 57.5 and 71.6, respectively. Similarly for C-21 (δ 59.3), which was linked to N-4. These assignments were in excellent agreement with the full HMBC data (Figure 1). The H-3 to C-13, C-2, and C-5 correlations were consistent with branching of C-3 from N-1 (and N-4), while the H-21 to C-3 and C-5 correlations were consistent with the connection of C-21 to N-4.

Examination of the vicinal coupling constants ($J_{5\beta\text{-}6\alpha}$, $J_{3\alpha\text{-}14\beta}$, $J_{14\beta\text{-}15\alpha}$, $J_{15\alpha\text{-}16\beta}$, $J_{16\beta\text{-}17\alpha}$, $J_{17\alpha\text{-}18\beta}$, $J_{18\beta\text{-}19\alpha}$, $J_{19\alpha\text{-}20\beta}$, $J_{20\beta\text{-}21\alpha}$ ∼ 11−14 Hz) and the NOE data (Figure 3), indicated that the C, D, and

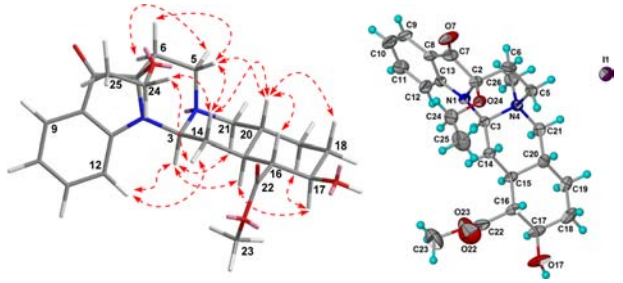
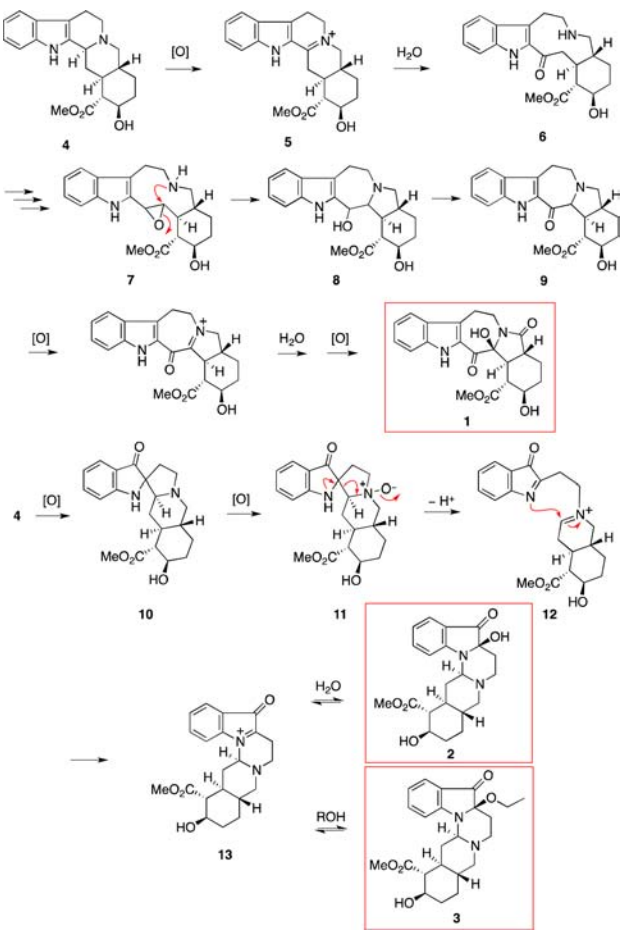


Figure 3. Selected NOEs of **3** and X-ray crystal structure of **3a**.

E rings adopted the stable chair conformations, with *cis*-fused C/D and *trans*-fused D/E rings, and with the C-16 methyl ester and C-17 OH groups oriented equatorially. The C/D *cis*-ring fusion was also supported from the X-ray diffraction data of the methyl iodide salt of **3** (**3a**, Figure 3).[17] The ethoxy group was deduced to be β-oriented from the observed H-24/H-14 NOEs and from its presumed origin, which required the alcohol nucleophile to approach the precursor iminium ion from the less hindered β-face (Scheme 1). Vernavosine (**2**) represents another novel monoterpenoid indole alkaloid skeleton,

Scheme 1. Possible Biogenetic Pathways to 1 and 2/3 from 4



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characterized by incorporation of a pyridopyrimidine moiety embedded within a pentacyclic ring system.

We propose that both alkaloids originate from a common β-yohimbine precursor **4**, which was among the alkaloids present in the plant (Scheme 1). Thus, hydrolytic cleavage of the iminium ion **5** derived from oxidation of the β-yohimbine precursor **4** gave the keto amine **6**. Reduction of the ketone function, followed in succession by dehydration and oxidation, yielded the epoxide **7**. Epoxide ring opening via transannular attack by the secondary amine nitrogen forged the pyrroloazepine ring system of the alcohol **8**, which on selective oxidation of the benzylic alcohol moiety gave the conjugated ketone **9**. Nucleophilic attack by water on the iminium ion derived from **9** installed the tertiary alcohol functionality at C-14, and a final oxidation provided criofolinine (**1**). Alternatively, oxidation of the same β-yohimbine precursor **4** gave the pseudoindoxyl alkaloid **10**. A further oxidation provided the *N*(4)-oxide derivative **11**, which on a lone-pair assisted Grob-like fragmentation (Polonovski-like) yielded the imine-iminium ion intermediate **12**. Ring closure via attack of the imine nitrogen (N-1) on the iminium ion forged the new pentacyclic ring system of vernavosine in the form of its iminium ion **13**, which on reaction with water yields the carbinol amine **2**. In the presence of the stronger ethanol nucleophile,[18] the carbinol amine **2** will in all probability be readily converted to its ethanolysis product **3**, which was the final form of the alkaloid isolated. Hydrolysis of **3** (in two-phase medium with phase-transfer catalysis) gave the putative precursor alkaloid, the carbinol amine **2**, while re-exposure of **2** to EtOH in the presence of a trace of acid gave **3**, providing additional confirmation for the origin of the ethyl ether derivative **3** from the original intact alkaloid **2**.[19]

Both compounds **1** and **3** showed no appreciable cytotoxicity against drug-sensitive as well as drug-resistant KB cells, HCT-116, PC-3, and A-549 cells (IC_{50} > 25 μg mL^{-1} or 60 μM). Compound **3** however, showed a moderate concentration dependent relaxation effect on phenylephrine-induced contraction in isolated rat aortic rings with EC_{50} = 2.48 μM and E_{max} = 39.4 ± 4.4% (cf. isoprenaline, EC_{50} = 0.07 μM and E_{max} = 79.7 ± 4.2%).[20]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, NMR spectra, HRESIMS (**1**–**3**), and X-ray crystallographic data (CIF) of **1** and **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) HRESIMS found *m/z* 399.1550 $[M + H]^+$ (calcd for $C_{21}H_{22}N_2O_6$ + H, 399.1551).

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(14) The crystals of **1** are orthorhombic, belonging to space group $P2_12_12_1$, with *a* = 10.7249(5) Å, *b* = 12.1181(6) Å, *c* = 29.2040(13) Å, *V* = 3795.5(3) $Å^3$, *T* = 150 K, D_{calcd} = 1.394 mg/mm^3, and *Z* = 4. The final R_1 value is 0.0492 (wR_2 = 0.1440) for 7804 reflections [$I > 2\sigma(I)$]. CCDC No. 1029243.

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(16) HRESIMS found *m/z* 415.2233 $[M + H]^+$ (calcd for $C_{23}H_{30}N_2O_5$ + H, 415.2227).

(17) The crystals of **3a** are monoclinic, belonging to space group $P2_1$, with *a* = 10.4239(2) Å, *b* = 8.4186(2) Å, *c* = 14.8476(3) Å, *V* = 1273.54(5) $Å^3$, *T* = 150 K, D_{calcd} = 1.451 mg/mm^3, and *Z* = 2. The final R_1 value is 0.0382 (wR_2 = 0.1011) for 5866 reflections [$I > 2\sigma(I)$]. Flack parameter [*x* = 0.018(15)], Hooft parameter [*y* = 0.008(17)]. CCDC No. 1029244.

(18) EtOH was used during extraction of alkaloids.

(19) Compound **2**: $[\alpha]^{25}_D$ −62 ($CHCl_3$, *c* 0.06); HRESIMS found *m/z* 387.1914 $[M + H]^+$ (calcd for $C_{21}H_{26}N_2O_5$ + H, 387.1914); UV (EtOH), λ_{max} (log ε) 234 (3.48), 2.57 (2.91), 397 (2.59) nm ; ^1H and ^{13}C NMR, see Tables 1 and 2.

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